

Rebuilding the human brain

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Creating new organs from the correspondent primordia is the goal of organogenesis in transplantation medicine (Hammerman, 2005). Unlike embryonic stem cells, primordia differentiate along defined organ-committed lines and steered differentiation is unnecessary. Rebuilding human brain structures through in situ organogenesis is a real clinical working hypothesis of our time. The challenge of such an approach is that a grafted primordium recapitulates the ontogenesis without neoplasia/teratoma or overgrowth, generates proper circuits, and establishes connections with the host. We previously showed the generation of new tissue with neostriatal-like morphological features after transplantation of human striatal fetal tissue in five Huntington's disease (HD) patients, whose clinical course was positively affected by grafting (Gallina et al., 2008; 2010). These findings were interpreted as the capacity of neuroblasts to continue their development in the host. Here, we show some of the steps of the primordium growth in the brain of a further grafted HD patient and analyzed those intrinsic regulatory factors that may have played a role in promoting its development. The primordium graft expressed various neurotrophic factors, enriched with seladin-1, and also showed high levels of huntingtin. Moreover, the graft expressed a high level of neural recognition molecules and integrins, proteins that are involved in cell recognition function. Neuroblasts expressed connexin43-rich gap junctions. The presence of such proteins, which are involved in the intercellular communication process, indicates the potential of neuroblasts to establish graft-host connections. Currently, a real graft-host integration cannot be demonstrated. However, the establishment of some cellular connections is suggested by the results of cerebral metabolic imaging, which demonstrate not only the survival and longitudinal growth of the striatal grafts, but also a beneficial effect on distant cortical metabolism. Similarly, it is not clear whether the new structure works as a striatum or just has a striatal-like morphology. Nevertheless, the increase of D2 receptor binding at the striatal level suggests that the new structure sustains the striatal function and influences the patient's clinical course.

References

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